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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/741,550	12/19/2000	Julia Y. Ljubimova	18810-80364	6437

7590 10/16/2002
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EXAMINER

GOLDBERG, JEANINE ANNE

ART UNIT	PAPER NUMBER
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1634

DATE MAILED: 10/16/2002

8

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/741,550

Applicant(s)

LJUBIMOVA ET AL.

Examiner

Jeanine A Goldberg

Art Unit

1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 July 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-10, 13-18, 21-29, 32-36, 44, 45, 48-68 and 75-78 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-10, 13-18, 21-29, 32-36, 44, 45, 48-68 and 75-78 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

1. This action is in response to the papers filed July 22, 2002. Currently, claims 1-10, 13-18, 21-29, 32-36, 44-45, 48-68, 75-78 are pending.

Election/Restrictions

2. Applicant's election without traverse of Group II (Claims 1-10, 13-18, 21-29, 32-36, 44-45, 48-68, 75-78) in Paper No. 7 is acknowledged.

Specification

3. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

For example, page 20, line 2, a link is included.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-10, 13-18, 21-29, 32-36, 44-45, 48-68, 75-78 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are broadly drawn to methods for detecting any malignant tumor in a human subject by comparing the expression level of laminin alpha4-specific mRNA to normal controls, wherein overexpression of laminin alpha4-specific mRNA indicates the presence of a malignant tumor.

The art, namely Ringelmann et al. (Experimental Cell Research, Vol. 246, pages 165-182, 1999) teaches strong interstitial expression of laminin alpha4 mRNA in myogenic tissues of embryonic but not mature mice, implicating a role for this laminin alpha chain in myogenesis (page 166, col. 2). Additionally, Previtali et al. (Glia, Vol. 26, pages 55-63, 1999) teaches the abnormal expression of a laminin receptor, alpha6beta4 integrin in human astrocytomas (abstract). Tysnes et al. (Int. J. Devl. Neuroscience, Vol. 17, No. 5-6, pages 531-539, 1999) teaches "compared to normal astrocytes, neoplastic astrocytes in situ have shown increased expression of the laminin receptor alpha3 and beta1 integrin subunits" (page 538).

The specification asserts "malignant tumor tissues, such as glioblastoma multiforme (GBM) tissue and particularly vascular tissue of malignant tumors, overexpress the gene encoding laminin alpha4 subunit ... compared to weak expression in normal tissue, benign tumor tissue (e.g., meningioma) and lower grade malignant tumors (e.g., astrocytoma grade II)" (page 11 of specification). The drawings provide data which illustrates expression levels of laminin alpha4 subunit in brain tissue. Figure 5 illustrates "semiquantitative RT-PCR analysis of expression in brain tumors. Lanes 1-10 are directed to primary GBM tumor and adjacent tissue to the GBM. Lanes 11-15 appear to be normal or benign tissues. The astrocytoma grade II appears to have

the same expression as the malignant tumors. Table 3 provides the expression of structural genes. Laminin alpha4 chain is analyzed for GBM Grade IV, Adjacent to GBM and Astrocytoma Grade II. The values for expression are 3.8, 3.7 and 2.0 respectively. Figure 7 illustrates the laminin subunit expression. The figure demonstrates the differential expression in normal as compared with GBM or astrocytoma grade II tissues. Moreover, Table 7 provides information regarding the distribution of alpha4 chain in human brain tumor tissue compared to normal brain tissue. Patient 39 appears to have the same relative expression, namely +++, for both the GBM (malignant tumor) and for the relatively normal adjacent tissue. The relatively normal tissue of patient 39 appears to have more expression than the astrocytoma grade II and III which has either ++ or +/++. The specification teaches that "All GBMs and their adjacent tissues highly expressed laminin alpha4 subunit gene. Meningioma from patient 38 and normal brain from patient 46 had lower levels of laminin alpha4 subunit gene expression than glial tumors, but higher than normal brain from Patient No. 44 and corpus callosum" (page 49, lines 9-13). Therefore, the overexpression in a tumor as compared to a normal control would not necessarily be indicative of malignant brain tumor. It is unclear whether normal brain and corpus callosum are considered the control or whether normal brain from patient 46 would be considered the control. Therefore, there is no predictable correlation between the qualitative expression analysis provided in the specification and detection of malignant tumors. All of the analysis for expression of laminin alpha4 in brain tissue is qualitative and there is no evidence of statistically significant association. The ranges for "normal" and "malignant tumor" expression of

alpha4 have not been provided. There is no indication in the specification of a threshold which could be indicative of malignant tumors, namely brain tumors. Therefore, distinguishing a malignant tumor tissue from a normal tissue based solely on different sample expression would be unpredictable.

With respect to Claims 28-29, 32-36, 44-45, 48-59 directed to a method of predicting the recurrence of a malignant tumor in a human from whom a tumor has been resected, the fails to provide any analysis directed to recurrence of a malignant tumor. The specification does not provide any predictable correlation between recurrence of a malignant tumor and expression analysis. While the skilled artisan could provide an analysis of region adjacent to the site of the tumor and analyze their expression of laminin alpha4, the results of such experiment would be unpredictable.

With respect to Claims 60-66 directed to method of classifying the grade of a malignant tumor by comparing expression profiles, the specification has provided no guidance to classification. The specification has provided no guidance as to what the "relatively high invasiveness of the tumor" encompasses. The specification seems to illustrate a few examples where laminin alpha4 is overexpressed in astrocytoma grade II. The specification teaches that astrocytoma grade II is a lower grade malignant tumor (page 11, lines 15-16). Therefore, it is unclear how the overexpression of laminin is indicative of relatively high invasiveness of the tumor. The claims does not appear to make any distinction between low grade and higher grade tumors. Therefore, it is unclear how the tumors are classified. While the skilled artisan could provide further undue experimentation to determine a value for expression in the various types of

tumors and obtain thresholds for classifying the tumors, the instant specification does not provide any predictive correlation between thresholds and classifications of tumors into grades, as required by the claims.

Moreover, the specification provides no guidance to the skilled artisan how to use the invention with respect to any type of malignant tumor. The specification does not teach expression levels in all malignant tumors, including breast, prostate, lung, colon, etc. While one could conduct additional experimentation to determine whether, e.g., overexpression of laminin alpha4 might be associated with, e.g., additional malignant tumors, the outcome of such research cannot be predicted, and such further research and experimentation are both unpredictable and undue. In the absence of guidance from the specification, one skill in the art may look to the teachings of the prior art for enablement of a claimed invention. However, the closest prior art references, do not provide support for the use of laminin alpha4 expression as an indicator of malignant tumor. Thus is is unpredictable as to whether one could successfully use the claimed invention, and given the fact that neither the specification nor the prior art provide evidence of a correlation or association between laminin alpha4 expression and malignant tumors, it is further unpredictable as to whether any quantity of experimentation would allow one to practice the claimed invention. Accordingly, it would require undue experimentation for a skilled artisan to use the claimed invention.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 9-10, 60-66 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 9 is indefinite over the recitation "the neoplastic growth" because Claim 1, from which Claim 9 depends does not refer to a neoplastic growth. Therefore, the recitation "the neoplastic growth lacks proper antecedent basis. Appropriate correction is required.

B) Claim 10 is indefinite over the recitation "the hyperplastic and/or cytologically dysplastic cellular growth or proliferation" because the recitation lacks proper antecedent basis. Claim 1 does not refer to hyperplastic and/or cytologically dysplastic cellular growth or proliferation. Appropriate correction is required.

C) Claims 60-66 are indefinite over the recitation "relatively high invasiveness". The term "relatively high invasiveness" in claim 60 is a relative term which renders the claim indefinite. The term "relatively high invasiveness" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Furthermore, the preamble is directed to a method of classifying the grade of a malignant tumor, however the final process is directed to indicating the presence and relatively high invasiveness of the tumor. The claims does not provide any means for classifying the grade of a malignant tumor. Classification generally requires placing the items into several different categories. The claims provide no guidance to how to

classify the grade of a malignant tumor. Therefore, it is unclear whether the claim is directed to classifying the grade of a malignant tumor or whether the claim is directed to predicting "relatively high invasiveness". The metes and bounds of the claimed invention are unclear.

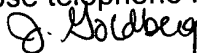
Conclusion


6. No claims allowable.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.


Jeanine Goldberg
October 9, 2002


W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600